

## REMARKS

Upon entry of the present amendment, claims 1-3, 5, and 12-18 are pending. Claims 4, and 6-11 are cancelled without prejudice or disclaimer. Applicants reserve the right to pursue cancelled subject matter in one or more continuing or divisional applications. No new matter has been added.

### **Double Patenting**

Claims 1-3, 5, and 12-18 are rejected on the ground of nonstatutory obviousness-type double patenting over U.S. Patent No. 7,138,390. Although the Applicant disagrees with the Examiner, in the interest of expediting prosecution of the instant application, the Applicant has filed herewith a terminal disclaimer disclaiming the term of a patent issuing from the present application that extends beyond the expiration date of U.S. Patent No. 7,138,390. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 1-3, 5, and 12-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over copending U.S. Patent Application Nos. (a) 11/081,002, (b) 11/602,307, and (c) 11/914,559. Applicant will consider filing a terminal disclaimer upon notice of allowable subject matter in these applications or the instant application.

### **Claim Rejections Under 35 U.S.C. § 103**

The Examiner has maintained the rejection of claims 1-3, 5, and 12-18 under 35 U.S.C. § 103(a) over Frigerio et al. (EP 312,867) ("Frigerio"). Applicant traverses the rejection.

The Office Action alleges that, in view of Frigerio, the instant compound is obvious because the Examiner states that the prior art teaches the adjacent lower homolog and, thus the skilled artisan would have the reasonable expectation that compounds with a similar structure differing in only a single -CH<sub>2</sub>- would have similar properties. The Examiner cites the 1950 case *In re Henze* stating that the court has held that adjacent homologs are obvious absence [*sic*] a showing of unexpected and/or unobvious results. *See*, page 7 of the Office Action.

Applicant asserts that the test for establishing obviousness of similar compounds requires more than just a showing of a structural similarity of the prior art and the claimed compound.

Applicant asserts that the cited Frigerio reference does not provide such additional information or rationale.

The Federal Circuit in *Takeda Chemical Industries v. Alphapharm Pty.* recently discussed the test for establishing the prima facie obviousness of similar chemical compounds. 492 F.3d 1350 (Fed. Cir. 2007). Noting that their “case law concerning prima facie obviousness of structurally similar compounds is well established,” the court stated:

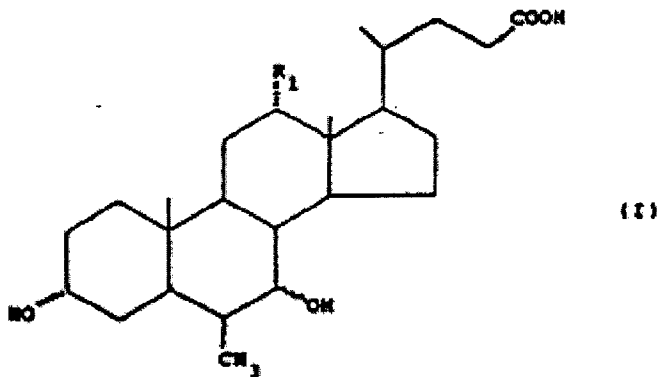
In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of “adequate support in the prior art” for the change in structure.... [I]n order to find a prima facie case of unpatentability in such instances, a showing that the “prior art would have suggested making the specific molecular modification necessary to achieve the claimed invention” [is] also required.

*Id.* at 1356 (citations omitted). The court continued by saying that the above “test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in” the Supreme Court’s recent decision of *KSR Int’l v. Teleflex Inc.*, 550 U.S. \_\_\_\_ (2007), 127 S. Ct. 1727 (2007). *Id.* Therefore, the court concluded that “in cases involving new chemical compounds, it remains necessary to identify some **reason** that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.” *Id.* at 1357 (emphasis added).

The Office Action presents no reason as to why one of ordinary skill in the art would separate Frigerio’s mixture of compounds, select a specific diastereomer and modify it to arrive at the claimed invention. Applicant submits that the claimed compound differs from the mixture of compounds in Frigerio in three respects: to arrive at the claimed invention, one would have to separate the mixture of compounds disclosed in Frigerio, select the particular diastereomer with the 6-methyl group in the alpha configuration, and then homologate the 6-alpha-methyl group to an ethyl group. Frigerio fails to provide any reason explicitly or implicitly that would lead the ordinarily skilled artisan to separate the mixture of compounds taught therein, select one particular diastereomer and modify it in order to reach the instant invention. As such, Applicants contend that the Examiner has failed to establish a prima facie case of obviousness and the rejection over Frigerio is improper.

Frigerio fails to explicitly or implicitly teach or suggest the claimed invention. The claimed invention is a single diastereomer, 3 $\alpha$ -7 $\beta$ -dihydroxy-6 $\alpha$ -ethyl-5 $\beta$ -cholan-24-oic acid, with the ethyl group at the 6-position in the  $\alpha$ -configuration and the hydroxyl group at the 7-

position in the  $\beta$ -configuration. *See*, Specification at page 3, Brief Summary of the Invention, Examples 1-3 and Claim 1. Rather, Frigerio teaches a mixture of methyl-substituted compounds of formula I, wherein  $R_1$  is hydrogen or hydroxyl, and the stereochemistry of the methyl and hydroxyl groups at the 6- and 7- positions is not specifically defined as shown by the wavy bonds (lines) in formula I:



The Applicant submits that one of ordinary skill in the art readily envisions formula I as comprising a mixture of at least four distinct chemical species wherein the configuration at the 6 and 7 positions is: 6 $\alpha$ -Methyl/7 $\alpha$ -Hydroxy, 6 $\beta$ -Methyl/7 $\beta$ -Hydroxy, 6 $\alpha$ -Methyl/7 $\beta$ -Hydroxy, and 6 $\beta$ -Methyl/7 $\alpha$ -Hydroxy. Further, the final product prepared in Example 3 of Frigerio, 3- $\alpha$ -7- $\epsilon$ -dihydroxy-6-methyl-5-B-cholan-24-oic acid is a mixture of diastereomers. Frigerio does not teach or suggest any method to separate the compound mixture of formula I or any benefit of selecting a single diastereomer over the mixture of compounds disclosed e.g., Frigerio does not suggest any functional differences between the compounds comprising the mixture, preferred structural configurations at the 6- and 7-positions, or superior properties or unexpected results of a single diastereomer with respect to either Frigerio's intended purpose or the FXR agonist activity of the compound of the instant application.

The Applicant further asserts that Frigerio does not teach or suggest substituting the methyl group at the 6-position with any other function group, and, in fact, Frigerio teaches that the presence of the methyl at this position is a defining characteristic of the mixture of compounds. *See*, Frigerio at page 3, lines 41-46. Specifically, Frigerio states, "...the compounds of the present invention...are characterized by the presence of a methyl group at 6-position....The methyl group at the 6-position makes the molecule more hydrophobic and more liable to form micells..." (emphasis added). *Id.* Accordingly, Applicant submits that the skilled artisan reading Frigerio would not be motivated to modify the 6-methyl group, a group which

Frigerio identifies as being responsible for a key property. Applicant contends that the teachings of Frigerio in fact provide a negative motivation for the ordinarily skilled artisan to alter the methyl group at the 6-position because the change could disrupt the desired function.

Although the Examiner contends that similarity in chemical structure renders compounds with similar properties, Applicant asserts that chemical structure cannot predict function. Applicants submit that Frigerio and the prior art, as well as a declaration filed in U.S. Serial No. 10/471,549, now issued U.S. Patent No. 7,138,390, explicitly demonstrate that small changes to the bile acid structure result in dramatic changes in function. Importantly, these exemplary changes in structure are similar in scope to the proposed modifications to Frigerio's mixture that would be necessary to reach the instant invention. For instance, Frigerio teaches that UDCA, 3 $\alpha$ -7 $\beta$ -dihydroxy-5 $\beta$ -cholan-24-oic acid, a structurally similar compound to the compounds of Frigerio's mixture but which lacks the 6-methyl group, also lacks the desired special properties of increased hydrophobicity and increased liability to form micells. *See, Frigerio* at page 3, lines 45-46. Further Applicant submits that this compound with a similar structure is also known in the art to be FXR silent i.e. UDCA completely lacks the agonist activity of the claimed invention. Li-Zhi Mi et al. (Molecular Cell, 2003, 11, 1093-1100)(“Li-Zhi Mi”).

To further support Applicant's assertion that structure can not predict function, Applicant directs the Examiner to the declaration filed in the U.S. case to which a terminal disclaimer is being filed herein i.e., U.S. Serial No. 10/471,549, now issued U.S. Patent No. 7,138,390 (“the ‘390 patent”). A copy of the ‘390 declaration is provided herewith, Exhibit A. In the ‘390 declaration, Applicant demonstrated that 6-Et CDCA (chenodeoxycholic acid) exhibited the unexpected and surprising result of being significantly more potent than other FXR ligands, including 6-Me CDCA. When the FXR binding potency and efficacy of 6-methyl-CDCA and 6-ethyl-CDCA, the compound claimed in the ‘390 patent, were compared, the concentration of the half-maximal response ( $EC_{50}$ ) was 0.75 $\mu$ g and 0.098 $\mu$ g, respectively. *See, Pellicciari Decl.* at ¶ 6 and Table 1 (filed in U.S. Patent No. 7,138,390). Thus, 6-ethyl CDCA bound FXR with approximately 8x the potency and efficacy as the 6-methyl derivative. Moreover, 6-ethyl CDCA of the ‘390 patent provides increased and superior affinity for FXR. Specifically, the affinity of 6-ethyl CDCA was 0.798 ( $10^{-EC_{50}}$ ) versus 0.178 for 6-methyl-CDCA. *See, Pellicciari Decl.* at ¶ 7 and Figure 1. Studies involving FXR transactivation in HepG2

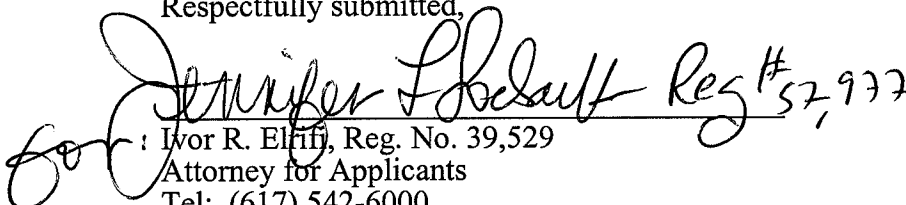
human liver cells revealed that 6-ethyl CDCA was more potent than the 6-methyl-CDCA. *See*, Pellicciari Decl. at ¶ 8 and Figure 2.

Consequently, the Applicant submits that because Frigerio fails to teach or suggest the claimed single 6-alpha-ethyl diastereomer and fails to provide any explicit or implicit motivation for separating Frigerio's mixture of 6-methyl compounds and selecting and modifying one specific diastereomer to reach the instant invention, the Examiner has not established a *prima facie* case of obviousness and the instant rejection over Frigerio is improper. Moreover, the Applicant submits that the foregoing arguments demonstrate that the skilled artisan reading Frigerio would not have selected and modified the mixture of 6-methyl compounds described by Frigerio to reach the instant invention with any reasonable expectation of predictable results. Provided the teachings of Frigerio in combination with the knowledge and state of the art, the Applicant contends that the ordinarily skilled artisan would have no objective reason to believe that any separation and modification of the mixture of compounds disclosed by Frigerio would create an FXR agonist. For all of the foregoing reasons, the Applicant submits that the instant invention is nonobvious over Frigerio. Reconsideration and withdrawal of the rejection is requested.

### CONCLUSION

On the basis of the foregoing amendment and remarks, Applicants respectfully submit, that the pending claims are in condition for allowance. If there are any questions regarding this amendment and/or these remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

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